ISBN 1188-4169

Canada Communicable Disease Report

FAX

Vol. 24-12

Date of publication: 15 juin 1998

Contained in this FAX issue: *(No. of pages: 5)*

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CONCURRENT BABESIOSIS AND LYME DISEASE DIAGNOSED IN ONTARIO

Introduction

Human babesiosis (caused by *Babesia microti*) and Lyme disease (caused by *Borrelia burgdorferi*) are among the most common tick-transmitted zoonoses. Recent evidence indicates that both diseases are emerging in the northeastern and Great Lakes regions of the United States as the deer tick (*Ixodes scapularis*), which transmits both infections, increases in geographic distribution[1,2]. Because *B. microti* and *B. burgdorferi* reside in the same rodent reservoir (*Peromyscus leucopus*) and are transmitted by the same tick vector, human co-infection may be relatively common in endemic areas. In support of this contention, up to two-thirds of Long Island residents with Lyme disease have antibodies to *Babesia* species[3]. However, until recently, only three episodes of co-infection had been described and, in each case, a particularly severe illness was experienced and one individual died[4-6]. A recent report from New England found that the severity of symptoms and duration of illness in patients with concurrent babesiosis and Lyme disease was greater than for either infection alone[7].

Ixodes scapularis ticks have been found in a number of provinces in Canada and 205 cases of Lyme disease were reported to public-health officials from 1984-1994 (105 locally acquired)[8]. However, there have been no previous reports of co-infections in Canada and, to our knowledge, no case of babesiosis has ever been reported in Canada. This report describes a co-infection of babesiosis and Lyme disease acquired by a Canadian traveler.

Case Report

A 59-year-old male from Toronto presented to The Toronto Hospital on 27 July 1997 because of persistent fever and night sweats. The patient had recently returned from a 6-week trip to Nantucket, where he had vacationed in a summer home. There was no history of rural travel nor hiking or walking in the woods. Additional travel history included a trip to Hong Kong, Indonesia, and Singapore 7 months ealier.

The patient was well until 21 June 1997 when he noticed a small black "pinhead" lesion on his left biceps, which he removed. He subsequently developed a spreading erythema surrounding this lesion that spontaneously resolved after 2 to 3 days. On 26 June, he experienced a 2-day episode of fever, sweats, chills, myalgia, and fatigue, which was treated symptomatically with acetaminophen. He was then well until 21 July 1997 when the fever and chills returned. In addition, he developed rigors, extreme fatigue, headache, myalgia, nausea, vomiting, and drenching night sweats. On 22 July, he saw his family physician who diagnosed a "viral infection". On presentation to The Toronto Hospital 5 days later, he was febrile (38.8° C), pale, and appeared ill. He had a tachycardia of 130 beats/minute, mild splenomegaly, and occasional petechia on his extremities. The remainder of his examination was unremarkable.

Initial laboratory investigations revealed a normochromic, normocytic anemia of 106 g/L, leukopenia of 4.2 billion/L (normal 4.5 to 11.0), thrombocytopenia of 14 billion/L (normal 150 to 400), elevated lactate dehydrogenase at 799 U/L (normal 45 to 90), bilirubin 26 µmol/L (normal 2 to 17), aspartate aminotransferase 151 U/L (normal < 35), fibrinogen 4.22 g/L (normal 1.5 to 3.5), fibrin degradable products > 10 µg/mL (normal < 2.5), international normalized ratio 4.89 (normal 1.00), decreased haptoglobin < 0.12 g/L (normal 0.6 to 2.9), and D-dimers < 250 ng/mL (normal 500 to 1,000). Urinalysis was positive for blood and hemoglobin.

His past medical history was significant for nephritis of unknown etiology at the age of 3 years, atrial fibrillation diagnosed in 1995, and a myocardial infarction in 1996 complicated by

congestive heart failure. He had not previously undergone splenectomy nor had he ever received a blood transfusion. The patient's medications included coumadin 7.5 mg po od, cozaar 50 mg po od, lanoxin 0.125 mg po od, and acetylsalicylic acid 325 mg po od. He had no known allergies.

His travel history to southeast Asia, fever, and hemolytic picture suggested malaria; thick and thin films were ordered. Thick and thin films revealed many tiny ring forms, initially interpreted as *Plasmodium falciparum* malaria at 4% parasitemia. However, an astute senior technologist noted morphologic differences from *P. falciparum* malaria and correctly identified the protozoan organisms on the smears as trophozoites of *B. microti*.

Given the severity of his illness and the preceding rash consistent with erythema migrans, there were concerns of a co-infection with additional tick-borne agents. Lyme serology was ordered and reported as positive by enzyme-linked immunoabsorbent assay and IgM positive by specific Western blot test indicating a recent infection with *B. burgdorferi*. Serology for human monocytic ehrlichiosis (HME), caused by *Ehrlichia chaffeensis*, was reported as negative at 1:64 by immunofluorescence assay. Polymerase chain reaction assays for the agent associated with human granulocytic ehrlichiosis (HGE), caused by *Ehrlichia equi*-like organisms, were performed in our laboratory and were negative[9].

The patient was treated with quinine 600 mg tid and clindamycin 600 mg tid for 7 days for the babesial infection and doxycycline 100 mg bid for 21 days for Lyme disease. He responded promptly to therapy and was smear negative by the fourth day. When seen in follow-up at 1 and 2 months, he was asymptomatic, all previous biochemical and hematologic abnormalities returned to normal, and smears for babesiosis were negative.

Discussion

This case represents the first description of human babesiosis and the first report of a co-infection with Lyme disease recognized in Canada. Human babesiosis in the northeast and Great Lakes regions of the United States is caused by *B. microti*, an intracellular parasite that may be confused with *P. falciparum* malaria both clinically and morphologically, as initially occurred in this case[10]. The morphologic features that permit discrimination from malaria include the presence of paired piriform stages and a tetrad configuration ("Maltese cross") formed by binary fission of the trophozoite to form four merozoites. These later forms are diagnostic for babesiosis but may be difficult to find. The absence of pigment and gametocytes in babesiosis may also be helpful distinguishing features. A new species of babesiosis (WA-1) which is morphologically identical to *B. microti* has been described on the west coast of the United States and in Missouri[11,12].

The nymph stages of *I. scapularis* are primarily responsible for transmission of both Lyme disease and babesiosis. The nymph is < 3 mm long even when fully engorged, and most infected persons do not remember a tick bite[13]. It is probable that the small pinpoint lesion removed by the patient in this case was in fact an engorged nymphal-stage tick. Nymphs typically feed more actively in May and June resulting in a peak of clinical illness in July. As in this case, symptoms of babesiosis usually begin 1 to 4 weeks after a tick bite[13]. The clinical spectrum ranges from a mild, self-limited illness to a serious life-threatening infection with severe hemolytic anemia, thrombocytopenia, renal failure and hypotension[13]. Mortality rates in the United States have been < 10%, and deaths more common in the elderly, those with splenectomy, and those with HIV infection[13,14].

Co-infection with other tick-borne agents has recently been recognized as an important determinant of the outcome of infection with babesiosis. The disease caused by the co-infection with both Lyme disease and babesiosis was shown decades ago to be more severe in experimental animals[15]. This observation has now been extended to human co-infections. Krause and colleagues reported that 11% of patients with Lyme disease in southern New England are co-infected with babesiosis[7]. Co-infected patients had significantly more fatigue, headache, sweats, chills, anorexia, emotional lability, nausea, conjunctivitis, and splenomegaly than those with Lyme disease alone. Furthermore, 50% of these patients were ill for ≥ 3 months compared to 7% with Lyme disease. This increase in the number and duration of symptoms may be attributed to immunosuppression associated with babesial infection[7,15].

Recently, immunoserologic evidence of co-infection with a third tick-transmitted bacterial zoonosis, *Ehrlichia* species (HGE and HME), has been reported[12,16,17]. In a sero-epidemiologic study of residents of Wisconsin and Minnesota, 9.4% of patients with Lyme disease had serologic evidence of co-infection: 5.2% with HGE, 2.1% with babesiosis, and 2.1% with both[16]. Similarly in Sonoma County, California, 23% of residents were seroreactive to antigens from one or more tick-borne agents: 1.4% to Lyme, 0.4% to HGE, 4.6% to HME, and 17.8% to babesia-like piroplasm WA-1[12]. These studies indicate that tick-borne diseases are widespread and prevalent in some regions of the United States. Travelers from Canada will be at risk when they visit these areas during tick season (generally from May to September in the northeast). Furthermore, *I. scapularis* ticks have been identified in approximately 250 locations in Canada[8]. Prolonged parasitemias that may accompany co-infection with babesiosis, or subclinical infection in Canadian travelers who acquire any of the tick-borne pathogens, may facilitate transmission of infection to *I. scapularis* ticks in regions of Canada where they reside[7]. Finally, blood products are not routinely screened for *B. microti* or *B. burgdorferi*. Babesiosis may be transmitted by blood transfusion and is a cause of febrile transfusion reactions in endemic areas[18,19].

In summary, malaria should always be considered in febrile travelers and in cases of fever of unknown origin, even in those without a travel history[20]. But clinicians should also consider babesiosis in the differential diagnosis of febrile travelers returning from enzootic areas of the United States where, during the tick season (May to September), infection with *B. microti* and *B. burgdorferi* is not uncommon. Furthermore, we suggest that all patients with a documented tick-transmitted infection be evaluated for co-infection with other known tick-borne agents, particularly if

symptoms are severe or persist after therapy. Given the current levels of travel between Canada and the United States, and the emergence of Lyme disease, babesiosis, and ehrlichiosis, we must anticipate an increase in the number of imported cases of these tick-borne pathogens in Canadians. Prompt recognition of cases, accurate identification, and appropriate initial management is crucial in reducing morbidity and mortality associated with these infections.

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Source: *C dos Santos, MD, K Kain, MD, Tropical Disease Unit, The Toronto Hospital and University of Toronto, Toronto, ON.*

International Notes

AN OUTBREAK OF RIFT VALLEY FEVER, EASTERN AFRICA, 1997-1998

In mid-December 1997, the Kenya Ministry of Health and the World Health Organization (WHO) in Nairobi received reports of 478 unexplained deaths in the North Eastern Province of Kenya and southern Somalia. Clinical features usually included acute onset of fever and headache followed by hemorrhage (bloody stools, vomiting with blood, and bleeding from other mucosal sites). Local health officials also reported high rates of spontaneous abortion and deaths from hemorrhage among domestic animals. This report describes the premilinary results of the subsequent outbreak investigation, including case description, and the results of a serologic survey.

The affected areas had experienced exceptionally heavy rains (60 to 100 times heavier than normal) that began in late October 1997 and continued into January, resulting in the worst flooding in the region since 1961. Initial diagnostic testing of 36 samples from humans at the National Institute of Virology, Sandringham, South Africa, and at the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, confirmed accurate infection with Rift Valley Fever virus (RVFV) in 15 samples (42%) through detection of IgM antibodies, virus isolation, and reverse-transcriptase-polymerase chain reaction (PCR) for viral nucleic acid immunohistochemistry.

Active surveillance conduction by the Kenyan Ministry of Health, WHO, and international relief organizations between 22 and 28 December 1997 in 18 villages in the Garissa district, North Eastern Province, Kenya (population 231,000), identified 170 deaths from a "bleeding disease". Severe flooding and large distances between settlements complicated case ascertainment and subsequent evaluation. Despite the geographic constraints, the surveillance system received reports and blood speciments from 231 cases of unidentified severe febrile illness, with onset dates from 25 November 1997 through 12 February 1998. The case definition was established as "self-reported or observed fever and mucosal or gastrointestinal bleeding". Of the 115 patients meeting this case definition 67 (58%) were male with a median age of 30 years (range: 3 to 85 years), and 27 (26%) were positive for acute RVFV infection as evidenced by serology or virus detection (Figure 1). Of the 116 persons who did not meet the haemorrhagic

Figure 1
Temporal distribution of hemorrhagic fever cases by etiologic diagnosis, November 1997-February 1998, Kenya and southern Somalia

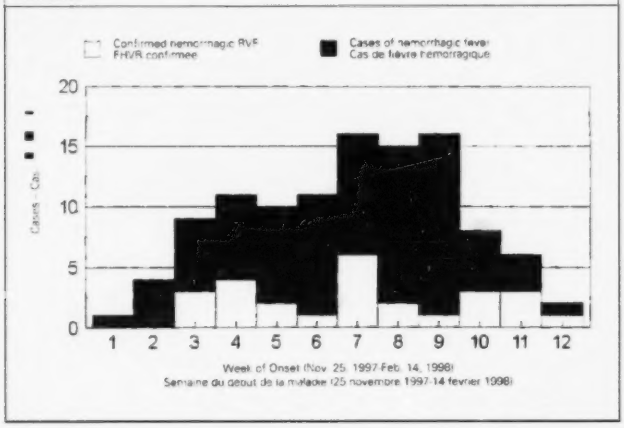
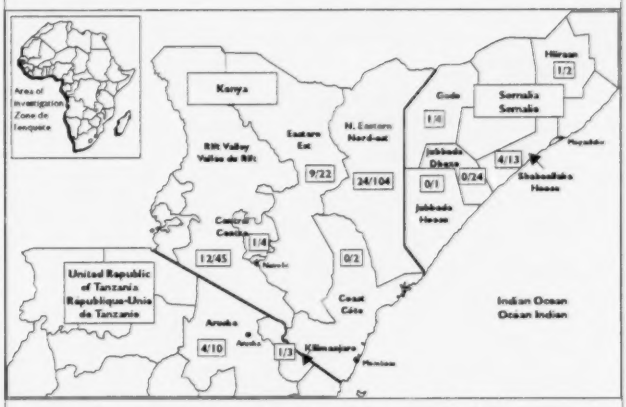


Figure 2
Geographic distribution of Rift Valley Fever outbreak, eastern Africa, 1997-1998*



* Number of confirmed cases/Number of cases with severe febrile illness reported to surveillance system

fever case-definition, 26 (22%) also had evidence of acute RVFV infection. Nine patients evidenced neurologic disease and five visual disturbances. In addition to the initial cases confirmed in the North Eastern Province of Kenya and Gedo, Hiran, and Lower Shabeelle provinces of Somalia, surveillance dentified cases from the Central (1 case), Eastern (9 cases), and Rift Valley (12 cases) provinces of Kenya (Figure 2).

Studies conducted in this outbreak included human, livestock, and entomologic sampling. Using a multi-stage cluster sampling strategy based on the population distribution in Garissa District, an international task force led by the Kenyan Ministry of Health conducted a cross-sectional study to establish the prevalence of recent RVFV infection and to examine risk factors for infection. Of the 202 participants, 75% had flood waters enter their home and 52% were forced to relocate. Eighteen (8.9%) individuals in the sample were positive for anti-RVFV IgM; all had a history of recent illness. The study did not identify statistically significant differences or the presence of detectable IgM antibody. Contact with livestock including herding, milking, slaughtering, and sheltering animals in the home were statistically associated with serologic evidence of acute RVFV infection.

In the cross-sectional survey, livestock owners reported losses of approximately 70% of their animals. Other infections in the epizootic included non-specific pneumonia pasteurellosis, hemonchosis, pneumonica, contagious caprine pleuropneumonia, contagious pustular dermatitis, bluetongue, and mange. These diseases have contributed to the high mortality observed among animals; many were complications linked to prolonged standing in muddy floodwaters. RVFV serologic results from samples collected by Kenyan veterinary staff from animals in Garissa District and other regions of the country are pending. In early February, 3,180 mosquitoes from three trapping sites in Garissa District were collected as part of an entomologic study. Of the nine species captured, three have been previously implicated in RVFV transmission (*Anopheles coustani, Mansonia africana, and M. uniformis*). Involvement of these species in the current outbreak will be further investigated in ongoing viral isolation studies.

WHO Editorial Note: In 1931, RVFV was first isolated in Kenya and recognized as the etiologic agent for a zoonotic disease associated with abortions and perinatal mortality in sub-Saharan Africa, associated with significant perinatal mortality and abortions. The extension of the disease into Egypt for the first time in 1977-1978 was officially associated with an estimated 18,000 infections and 598 deaths, and almost universal abortion in pregnant ewes and death among lambs. Epizootics tend to occur periodically following heavy rains that flood natural depressions allowing the hatching of the primary vector and reservoir (*Aedes* spp. mosquitoes). High levels of viremia in animals lead to infection of secondary arthropod vector species and virus amplification in livestock with collateral transmission to humans. As noted in this outbreak, transmission to humans can also occur by contact with blood or body fluid from viremic animals. Disease among humans is usually characterized as a mild febrile illness; however, some (1% to 2%) infections may result in a fatal hemorrhagic fever or encephalitis. A higher proportion develop vascular retinitis with permanent loss of vision.

The magnitude of infection and economic losses of the current outbreak are difficult to gage. Preliminary estimates of deaths among animals and humans suggest this may be the largest reported outbreak of RVFV in Eastern Africa, and the first to be officially recorded in Somalia. On the basis of antibody prevalence data and the assumption that all persons living in the North Eastern Province of Kenya and southern Somalia were a risk for infection, the total number of human infections in the region is estimated to be 89,000. This does not include infections in the rest of Kenya and neighbouring countries. Possible explanations for the cases of fever with hemorrhage that were negative for RVFV include the use of an extremely sensitive case definition, improper sampling, poor handling and transport of samples, the existence of other

pathogens and toxins, and the complications of malnutrition. Persons with active disease did not undergo through clinical and laboratory investigations, and for many cases bleeding was not directly observed by a clinician. Preliminary laboratory results have confirmed other viral agents, malaria, shigella dysentery, and leptospirosis as explanations for some of the reported cases. Ongoing studies may help define the magnitude and identify additional etiologic agents associated with this outbreak.

Satellite and precipitation data document widespread high levels of rainfall with increases in vegetation compared with the same period from previous years. These conditions favour RVFV transmission throughout Kenya and the surrounding countries. This is consistent with reports of confirmed cases from at least four Kenyan provinces (North Eastern, Eastern, Central, and Rift Valley), southern Somalia, and northern United Republic of Tanzania. Deaths from acute hemorrhagic fever among humans and abortions in livestock have also been reported from bordering countries although no specimens were available for laboratory diagnostic testing. The extent of transmission and inevitability of recurring outbreaks emphasize the need to develop and validate methods to predict, prevent and treat RVFV. Longitudinal studies are required to validate remote sensing statellite data in order to target areas for animal vaccination, enhance animal and human surveillance activities, and facilitate prospective entomologic studies. Early identification of disease will allow testing of new antiviral therapies.

CHOLERA IN LATIN AMERICA

Many countries in the Region of Americas are experiencing unexpected outbreaks of cholera associated with extreme weather conditions brought by the arrival of the El Niño phenomenon. During 1998, the following countries have already reported cholera outbreaks: Bolivia (mainly in La Paz Department) 165 cases and 5 deaths; Honduras (La Mosquitia, Gracias a Dios Department) 280 cases and 13 deaths; Ecuador (mainly in Loja Province) 76 cases and 1 death; Peru (various departments) 16,705 cases and 146 deaths; Nicaragua (border area with Honduras) 336 cases and 16 deaths. It is expected that other countries in the Region will report increased cholera incidence in the coming months.

Preventive and control measures are being taken by the ministries of health of the affected countries. However, as the epidemic in Latin America enters its eighth year and with the added impact of El Niño, cholera will continue to challenge governments and health agencies; additional international resources for emergency preparedness and control measures will be needed this year. WHO/PAHO is working closely with countries in the Region to reactivate cholera preparedness and response plans.

Source: *WHO Weekly Epidemological Record, Vol 73, No 15, 1998.*

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Scientific Advisors	Dr. John Spika	(613) 957-4243
	Dr. Fraser Ashton	(613) 957-1329
Editor-in-Chief	Eleanor Paulson	(613) 957-1788
Assistant Editor	Nicole Beaudoin	(613) 957-0841
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Price per year:

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Premium subscription : $150.00 (plus applicable taxes) in Canada; $175 (U.S.) outside Canada.

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